

Challenges to Pediatric Cancer Drug Development

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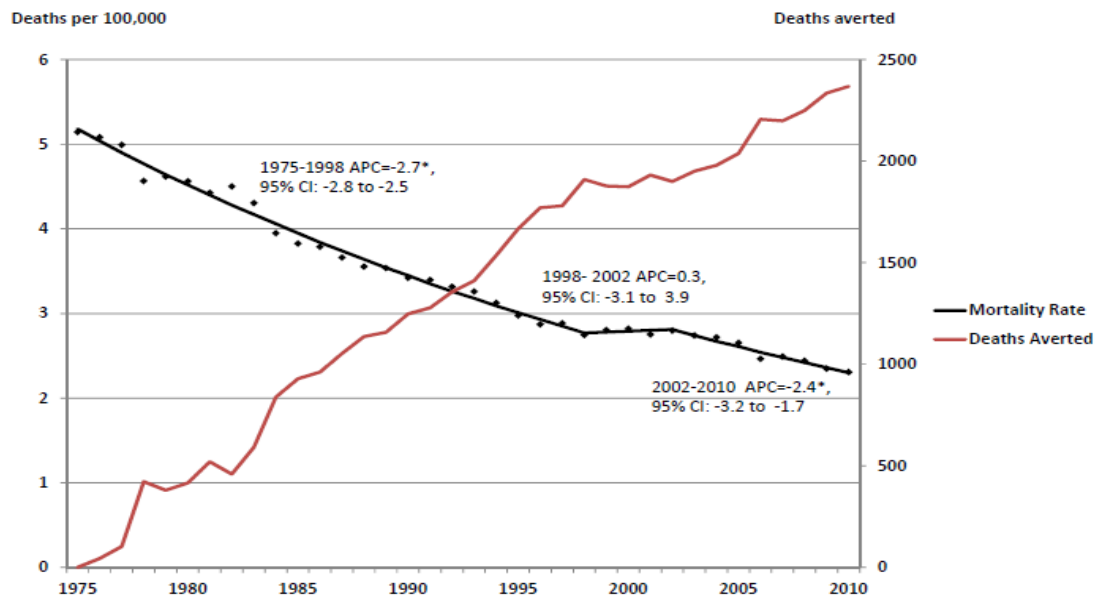
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Progress in Childhood Cancer

- Achieved through multi-center, multi-disciplinary, clinical and translational research
- Unique clinical practice/patient management model – highly integrated clinical care/clinical research
- Highly effective national clinical trials infrastructure
- Despite differences in biology, therapeutic product development has highly leveraged adult discovery/development

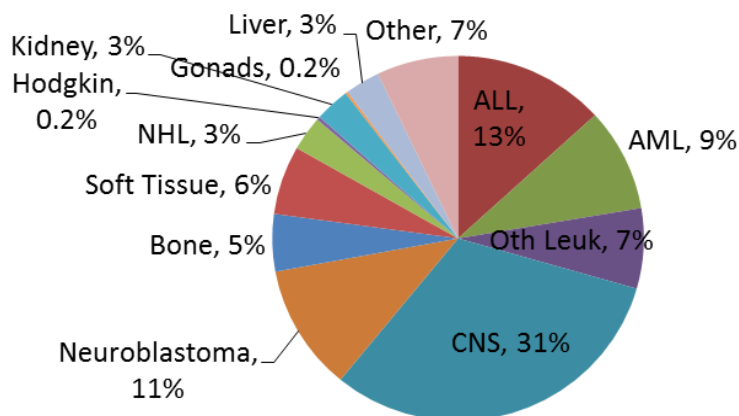
Childhood Cancer remains a problem



- Progress continues, but ...
- Nearly 2000 children continue to die each year,
- Advances not seen for some diseases and stages of disease
- Some of those who survive have reduced QOL due to the effects of their cancer and its treatment

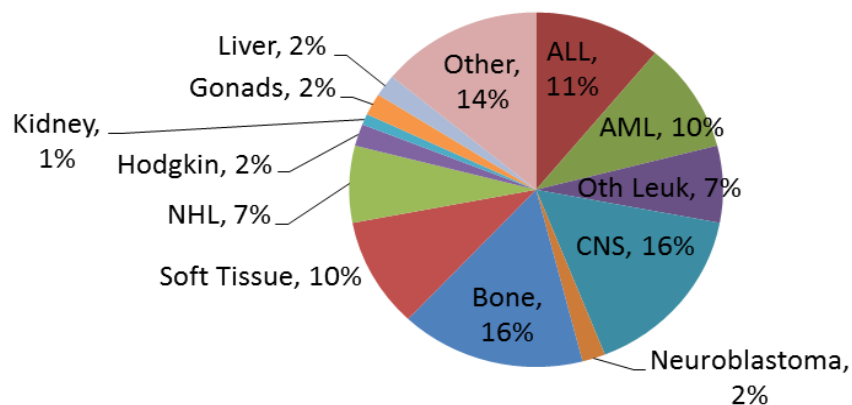
Childhood Cancer Mortality

<15 Year Mortality 2007-2010



~ 2000 children and adolescents die of cancer each year in the US

15-19 Year Mortality 2007-2010



Challenges to Therapeutic Research- Drug Development: Scientific and Pragmatic

- Low incidence disease (1% of U.S. Cancer diagnoses; 15,000/year)
- Small study populations for clinical trials
- Relative success of current treatments
- Pharmacology considerations and effect of normal development/maturation: organ function and metabolic enzyme

Challenges: (cont'd)

- Formulation requirements for pediatric use
- Current industry R&D models not favorable to pediatric drug development
- Insufficient pre-clinical models and testing programs
- Long term availability of promising products
- Different perspectives on “clinical benefit” – prolonging survival vs. cure
- Approaching cancer as a “chronic disease” – not a pediatric perspective
- Indication-driven PREA triggers – not relevant to cancer

Advances in Cancer Biology

- Unprecedented pace of discovery in genomic medicine and tumor biology → molecular pathogenesis of cancer
- Genetic mutations and amplifications involving key signaling pathways responsible for cell proliferation in specific cancers have emerged as validated targets for drug development
 - imatinib (Gleevec) in CML and Ph+ALL
 - crizotinib (Xalkori) in ALK+ NSCLC
 - vemurafenib (Zelboraf) in melanoma
 - Vismodegib (Erivedge) in basal cell carcinoma

Cancer Biology

- Multiple molecularly targeted therapies (53 as of 2/19/2015) approved for advanced stage or recalcitrant adult cancers based on favorable **benefit : risk** considerations – none yet demonstrated to be curative
26 of 53 completed/in progress/planned pediatric evaluations
- Personalized or PRECISION Medicine has largely benefited adults with cancer

Cancer Biology (cont'd)

- Molecular drivers (validated targets) of cancers are not universal for specific histologic types of cancer – multiple “orphan designations of what were once considered “common” adult cancers
- Genomic abnormalities are also not unique to specific histologic types and multiple biomarkers may exist for the same cancers “Master” (umbrella or basket) trials for genomically characterized tumors – Lung Cancer, Breast, NCI MATCH Trial

Progress in Childhood Cancer Genomics

- The vast majority of recurring genomic alterations for childhood cancers have been identified.
- This is the result of team science efforts led by groups such as the NCI TARGET Initiative, the St. Jude Children's Research Hospital - Washington University Pediatric Cancer Genome Project, and multiple others.
 - TARGET alone sequenced ~1,200 cases (primarily using WGS) and sequenced ~2,800 additional cases with frequency validation of 400 selected genes

Genomics Lessons Learned

- Childhood cancers have fewer gene mutations than adult cancers
- Many childhood cancers are driven by mutations that are rare in adult cancers:
 - Histone mutations for DIPG and high-grade glioma
 - Distinctive fusion genes for pediatric sarcomas and some brain tumors
- Many childhood cancers at diagnosis lack mutations in genes that are relevant to approved molecularly targeted agents or those being developed for adult cancers

Challenges in Childhood Cancer Research

- The (fortunately) relatively small numbers of patients with any specific cancer creates challenges in conducting clinical trials to reliably identify more effective treatments:
 - Complicated by further subdividing of diagnoses based on their genomic characteristics
 - Example of medulloblastoma: now being divided into 4 subtypes, each potentially with its own therapeutic strategy
 - Example of high-grade glioma: only 5-10% have BRAF genomic alterations; evaluations of BRAF inhibitors challenging for this population

Challenges in Childhood Cancer Research

- No obvious opportunities for prevention and early detection
- Relatively few driver mutations present at diagnosis that are addressed by currently available targeted agents.
- Known driver mutations of pediatric tumors have little interest to pharmaceutical companies:
 - EWS-FLI1 (Ewing sarcoma)
 - Histone K27 mutations (high-grade gliomas)
 - PAX-FKHR (alveolar rhabdomyosarcoma)

Addressing “Re-purposing” of Targeted Therapy to Facilitate Pediatric Drug Development

- Maximizing regulatory authority provided by current legislative initiatives to address “indication-based” “waivers”
- Rational prioritization of products to be evaluated
- Re-design of early phase studies toxicity-dose selection-activity signals- expansion cohort for efficacy
- Early communication/collaboration –
Investigators/Patients/Industry/Regulators

Maximizing Regulatory Authority

- FDASIA requirement for iPSP 60 days after EOP2 meetings
- Indication-based waivers planned (when targeted agent may be relevant to one or more pediatric cancers)
 - Sponsors requested to consult with academic investigators
 - BPCA Pediatric Oncology Working Group – Pediatric Subcommittee of ODAC – advise re: issuance of WRs

Maximizing Regulatory Authority (cont'd)

- WRs issued for oncology products:

1997-2013	51	2.5-3/yr
2014	7 new WRS	3 amended
2015	1	7 in progress

Addressing the Challenge of New Drug Development when No Adult Indication Exists

- No current legislative fix
- Substantial and early incentives to industry require expansion
- Continued success of current special initiatives (Pediatric Rare Disease Priority Review Vouchers) – subject to dilution of benefit and competing priority review mechanisms/“early” development incentive lacking
- Public/Private Partnerships – Role of NCI
 - Ch 14.18 (dinutuximab) in NBL
 - AMG479 in Ewing sarcoma

Opportunities for Precision Medicine in Pediatric Cancer

- ABL tyrosine kinase inhibitors in high risk ALL subpopulation (Ph+-like ALL)
- Pediatric MATCH (Molecular Analysis for Therapeutic Choice) Study
- Genomically-selected targeted agent approaches under development in neuroblastoma, medulloblastoma, and AML

Promising Approaches to Cancer Therapy: Role of Immunity

- Monoclonal Antibodies
 - BiTE (Bi-specific T-cell Engager)
- Immuno-conjugates (Brentuximab-vedotin, Adcetris)
- Enhancing host effector T-cell anti-tumor cell function
 - Check-point inhibitors – CTLA4 (ipilimumab, Yervoy)
 - PD1/PDL1 axis (pembrolizumab, Keytruda: nivolumab, Opdivo)
- Engineered cell therapy
 - CAR T-cells (CTL 019 and others)

Short-term/Long-term Safety (Toxicity) concerns: Continuing Challenges for Long-term Longitudinal Observation

- Targeted cancer agents are NOT non-toxic
- Unique effects on target tissues which depend on pathways being inhibited
- Heightened potential implications for children and developmental considerations

Acute and Potential Long-term Complications

- Diarrhea
- Fever, chills, asthenia
- Skin
- Cardiotoxicity, cerebrovascular, hypertension
- Pulmonary
- Ocular
- Musculoskeletal
- Neurologic
- Endocrine/reproductive
- Immunodeficiency/Autoimmunity

Short-term/Long-term Safety

- Insufficient long-term exposure data in adults
- Little combination toxicity data
- New organ targets and surveillance intervals needed
- A new paradigm for pediatric cancer LTFU
- Increased opportunities for industry collaboration to meet requirements for LT registry studies for toxicity

Patient-focused Drug Development

- A reality for children?
- Incorporating patient experience/perspective in changing benefit: risk assessment framework
- PROs/ObsROs: evidentiary standards to support treatment benefit claims
- Treatment Benefit: evidence of positive impact on a meaningful concept of interests: survival, disease-related symptoms, function in daily life

Challenges with Development of PRO Instruments in Children with Cancer

- Advice/input from ISPOR
 - Comprehension
 - Content validity/Domains of interest
 - Age appropriateness (8-11)
- Potential role for combined PRO and ObsRO data
- Limited early experience with qualification by SEALD team in plexiform neurofibromas

Challenges with Use of PRO/ObsRO endpoints in Pediatric Oncology

- Limited PRO labeling successes in oncology (symptoms/pain)
- Multi-domain concepts (QOL, Fatigue) – problematic
- Effect of concomitant meds
- Blinded and randomized trials required
- Objective and quantifiable measures
- More stakeholder input needed

Future Direction

- Pediatric Oncology – “Glass Half-full”
- Expand opportunities for evaluating Precision Medicine approaches to improve outcomes
- Paradigm shifts in study design, conduct, initiation, and F/U
- Rational science-based strategy for prioritizing which/when new products to test in what diseases; successful integration with “standard” therapy
- Expanded collaboration. Patients/families- Investigators – Industry – Regulatory Agencies ²⁶